Aus dem Institut für Anaesthesiologie
im Klinikum
der Universität Düsseldorf
Direktor: Prof. Dr. med. Martin Zindler

The mortality of surgical patients requiring mechanical ventilatory support.

DISSERTATION

zur Erlangung des Grades eines Doktors der Medizin

Der Medizinischen Fakultät der Universität Düsseldorf

vorgelegt von

Thomas Schürmann

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Mein besonderer Dank gilt
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Abstract.

The influence of three risk factors, progressed age, the duration of mechanical ventilation and the required F_IO_2, on the mortality was studied retrospectively in 279 surgical intensive care patients all requiring mechanical ventilation (MV) because of acute respiratory failure. An age $>$ 65 years, a duration of MV $>$ 10 days and a required F_IO_2 $\geq$ 0,5 were all associated with a marked elevation of the mortality above the average level of 56,6 %. A statistical estimation of the mortality if all three risk factors were present revealed an almost 99 % death rate. It is concluded that this might be useful information if the termination of life supporting intensive care measures is considered in patients with terminal illness.

Introduction

It has been shown in several studies concerning the prognosis of patients requiring mechanical ventilatory support that certain risk factors such as advanced age, the need for an elevated inspired oxygen concentration (F_IO_2), a prolonged duration of mechanical ventilation (MV) and associated organ dysfunctions indicate a severely compromised chance of survival.[1, 4, 5]

Under certain well defined conditions the presence of such factors may be taken in consideration in order to permit an appropriately timed termination of therapy and hence, avoid the inhuman torture of useless therapeutic an live support procedures. However, such decisions are a controversial matter because the criteria for termination of intensive care therapy including cardio-pulmonary resuscitation, parenteral nutrition, aggressive antibiotic treatment, renal dialysis, massive transfusion, major reoperative interventions, mechanical ventilation an others are still not sufficiently defined.

It has been demonstrated in the past that each of the above mentioned risk factors is associated with a mortality rate above the average level (US-ECMO-study). [4] The influence of a combination of several factors on the mortality has not been evaluated so far.

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F_IO_2 = fraction of inspired oxygen

This must be associated with a further increase of the mortality rate, hence, it should allow an improved prediction of the probability of death. Consequently it is the major purpose of this study to analyse the relationship between the combination of these risk factors and the mortality rates of patients requiring mechanical ventilatory assistance.

Materials and Methods

All patients of our surgical intensive care unit during a period of two years (1976/77) who needed MV via an endotracheal tube for at least 24 hours, were included in this study. These patients were analysed retrospectively for the type of primary disease, or operation, for the type of pulmonary disease, for age, for the duration of MV, according to the required F_IO_2 and for associated organ dysfunctions. In regard to the type of pulmonary disease patients were grouped similar to the classification of the US-ECMO-study [4] .

According to age, duration of MV and the required F_IO_2 patients were classified as follows:

(1) age: <10, 10 - 65 and >65 years,

(2) duration of MV: <5, 5 - 10 and >10 days,

(3) F_IO_2: $<0,5$ and $\geq 0,5$.

The following criteria were used to define associated organ dysfunction:

(1) renal dysfunction: a creatinin level > 2 mg %
(2) infectious disease problem: elevated body temperature ≧ 38,5°C, leukocytes count ≧ 13500 per mm^3, and according to postmortem findings.
(3) coagulopathy: laboratory evidence of consumption coagulopathy, postmortem thromboembolic findings.
(4) cardiovascular dysfunction: requirement for catecholamines.
(5) cerebral dysfunction: coma, seizures, paralysis (alone or in combination).

Intubation and controlled mechanical ventilation (MV) was instituted according to clinical, radiological an blood gas findings as established by Pontoppidan et al. and others. [8] Positive endexpiratory pressures were used either to treat acute arterial hypoxemia or to reduce the required F_IO_2 down to or below 0,5. Patients who needed more than a F_IO_2 = 0,5 without PEEP but less oxygen with PEEP were classified as requiring a F_IO_2 ≧ 0,5. Intermittent mandatory ventilation was not used at that time.
Clinical management was carried out according to accepted standards including early parenteral nutrition if nasogastric feeding was not possible, low dose heparin administration if consumption coagulo-

pathy was anticipated, substitution of clotting factors with fresh frozen plasma according to appropirate laboratory studies, and treatment with antibiotics according to clinical symptoms and microbiological findings.

Statistical methods

The relationship between the various risk factors and the mortality rate were analysed using the log linear model (BISHOP et al., 1975). The partial interactions between the various risk factors and the mortality rate were tested with the likelihood ratio test of partial interactions. The level of significance was taken at $\alpha = 0{,}05$.

The variability of the mortality rate depending upon the sample were expressed using 95 % confidence limits (c.l.).

They were determined independently for each table regardless of possible hierachical structures. The difference in the mortality rates of certain groups of patients should be real if the corresponding confidence limits did not overlap.

Results

A total number of 279 patients requiring mechanical ventilation for more than 24 hours (186 men and 93 women) were included in this study, 148 of these died

representing an overall death rate of 56,6 % (confidence limits 50 - 62 %). All patients were listed by the type of their primary disease or operation as indicated in table 1 and by the type of pulmonary disease as shown in table 2. Based on the hospital records a sufficient diagnosis of the pulmonary disease was possible in 193 cases, only.

The classification by the disease or the operative procedure revealed that the mortality was increased above the average level after gastrointestinal or vascular operations. In addition there was a group of patients with a 100 % mortality who had a variety of disorders which did not fit our scheme.

The kind of pulmonary disease did not allow any conclusions in regard to the mortality. The severety of the primary disease, e. g. heart disease was not evaluated.

Age

The patients were divided into three age groups (table 3). The mortality rose according to this classification reaching 96,7 % in patients older than 65 years. Between 10 and 65 years of age the mortality did not reveal a definitive trend.

Duration of mechanical ventilation (MV)

The relation between the duration of MV and the mortality is shown in table 4. The mortality rose with an increased duration of MV reaching 91 % after 10 days.

Required F_IO_2

The relation between the required F_IO_2 and the mortality is represented in table 5. Those patients who needed a $F_IO_2 \geq 0,5$ reached a mortality level of 87,6 % with relatively narrow confidence limits. Hence, a required $F_IO_2 \geq 0,5$ is highly indicative of a compromised prognosis.

Associated organ dysfunction

Tables 6 shows those patients who could be evaluated for pulmonary disease alone or plus at least one associated organ dysfunction or disease.
The most pronounced rises in mortality above the overall level were found due to the involvement of the kidneys.
A further rise in mortality was observed if in addition a required $F_IO_2 = 0,5$ was considered (table 6 b). Under these circumstances all except one patient with renal dysfunction (n = 31) died.

However, some of these groups as well as groups with a combination of associated organ dysfunction became too small to establish possible differences from the average mortality based on the confidence limits.

Combination of risk factors

Table 7 shows the distribution of patients according to the combination of the three risk factors: Age, duration of MV and the required F_IO_2. The application of the saturated log linear model to this table reveals that significant interactions between the three risk factors do not exist besides their independent influence on the mortality rate.
Figure 1 represents the mortality rates which result from the application of the above mentioned statistical model.
This illustrates the striking elevation of the mortality near 100 % if certain combination of risk factors are present, e. g. an age >65 or 10 - 65 years, a duration of MV >5 days and a required $F_IO_2 \geq 0,5$.

Discussion

Under clinical circumstances the type of pulmonary disease alone or in combination with another primary disease or surgical intervention often does not allow any useful prediction of the chances of death or survival.

Consequently factors not only related to the etiology but also to the pathophysiology must be taken in consideration. The criteria for this purpose must be simple to obtain, still reliable and applicable to all patients. [3, 9] It has been demonstrated by the analysis of the so called "additional data collection group" of the US--national-ECMO-study that those factors which were also the objective of our investigation are useful for such an improved judgement of the outcome in patients with acute respiratory failure. [4]

The findings of the present study can be listed as follows: the mortality of surgical intensive care patients requiring mechanical ventilation exceeding 24 hours was markedly increased above an average level of 56,6 %, if one of the following criteria was fulfilled:

(1) age > 65 years (96,7 % mortality, c.l.: 89 - 99 %, n = 31)

(2) a required $F_IO_2 \geq 0,5$ (87,6 % mortality, c.l.: 78 - 94 %, n = 75)

(3) a duration of mechanical ventilation > 10 days, (90,7 % mortality, c.l. 78 - 97 %, n = 43)

(4) pulmonary disease plus renal dysfunction (90,3 % mortality, c.l.: 82 - 96 %, n = 93)

All patients of the present population died if the following criteria were fulfilled:

(1) an age < 10 years plus a required $F_IO_2 \geq 0,5$ (n = 6)

(2) an age > 65 years plus a required $F_IO_2 \geq 0,5$ (n = 10)

(3) a required $F_IO_2 \geq 0,5$ plus infectious disease (n = 6).

If we compare our results with those of the US-national-ECMO-study [4] it appears that the overall mortality of our patients requiring mechanical ventilation for at least 24 hours was lower (56,6 %, n = 243) than in the "additional data collection group" of the ECMO-study (66 %, n = 686) and in a group of internal medical patients evaluated by HALBRITTER et al. [5] (70,7 %, n = 157). These difference are probably explained by the fact that those other groups consisted of more patients with severe acute pulmonary disease as for instance viral pneumonia, aspiration pneumonitis or with underlying chronic obstructive pulmonary disease than ours.

Obviously advanced age does increase the mortality also in mechanical ventilated patients. However, this became evident only beyond the age of 65 years which is in agreement with the findings of the US-ECMO-study. The patients studied by HALBRITTER et al showed already a progession of the death rate beginning with the forth decade of life. On the other hand more of their elderly patients survived than in our group of patients.

The duration of mechanical ventilation was also associated with a rise in mortality reaching 90 % (n = 38) after 10 days which was similar to the group of HALBRITTER et al. (86,5 %, n = 37). [5]

The F_IO_2 which is required during mechanical ventilation in order to achieve an arterial pO_2 of 60 - 80 mm Hg is a reflection of the degree of

ventilation-perfusion abnormalities in the lungs. The need for a higher F_IO_2 than 0,5 is a sign of a large intrapulmonary right -to-left shunt provided the patients conditions is not complicated by a low cardiac output or an increased O_2-consumption. The prolonged need for a $F_1O_2 \geq 0,5$ normally represents severe acute lung disease as for instance congestive atalectasis, capillary leak syndrome with pulmonary edema, pneumonia etc, and it indicates a significantly reduced chance of survival. Consequently it was not surprising that the need for an elevated F_IO_2 was associated with the most pronounced elevation of the observed mortality level (table 5).
The severity of acute lung disease also correlates with an elvated alveolar-arterial O_2 gradient (A-a D O_2). This was utilized in two previous studies concerning the mortality predicition in patients suffering from acute respiratory failure by Bartlett et al. [1] and by Hill et al. (1975). [6] Both groups of investigators achieved an improved predicition of the mortality based on a graphical analysis of the A-a D O_2 versus time. Although these graphical evaluations are relatively simple they seemed still to be too complicated in order to be generally accepted.

In contrast to previous studies we also evaluated the combination of the three risk factors relative to the mortality rate. This analysis was undertaken using a first order log linear model [2] which allows an estimation of the mortality rates under these circumstances (fig. 1). It shows that the presence of several risk factors is associated with a marked further increase in the probability of death as compared to a situation if a single risk factor is considered, only. However the groups of patients which were the basis for this analysis were still to small to allow a reliable prediction of death.

In conclusion, the combination of certain risk factors such as progressed age, the prolonged duration of mechanical ventilation, the need for an increased inspired O_2 - concentration does indicate a high probability of death. This can be taken in consideration if the continuation of intensive therapy is questioned, for instance in patients suffering from infectious endotoxemia or malignant disease. However, the present eveluation of these risk factors alone do not allow a reliable prediction of death in the individual patient. [7]

Table 1. Patients classified by primary disease or operation.

			died	%	(confidence limits) %
Thoracic disease	166	(59,9 %)			
Cardiac operations:					
Congenital } heart disease	59		17	28,8	(18 - 42)
Acquired } heart disease	90		36	40,0	(30 - 51)
Lung operations	9		4	44,4	(14 - 79)
Others	8		2	25,0	(3 - 65)
Abdominal disease	63	(22,6 %)			
Gastro-intestinal operations	31		27	87,1	(70 - 96)
Vascular operations	22		21	95,5	(77 - 99)
Others	10		6	80,0	(44 - 97)
Multiple trauma	38	(15,6 %)	21	55,3	(39 - 71)
Others	12	(4,3 %)	12	100,0	(73 -100)

Table 2. Type of pulmonary disease (according to classification of the US-ECMO study)

	n	died	%	(confidence limits) %
pneumonia	101	61	60,3	(50 - 69)
pulmonary capillary leak syndrome	52	39	75,0	(61 - 86)
pulmonary edema	29	13	44,8	(27 - 64)
chronic obstuctive pulmonary disease	5	3	60,0	(15 - 95)
thrombembolism	6	3	50,0	(12 - 88)
	193	119	61,7	(54 - 69)

Table 3. Age relative to mortality

years	n	died	%	(confidence limits) %
0 - 9	36	10	27,7	(14 - 45)
10 -65	212	108	50,9	(49 - 64)
>65	31	30	96,7	(89 - 99)

Table 4. Duration of mechanical ventilation relative to mortality

days	n	died	%	(confidence limits) %
1 - 4	160	59	36,8	(29 - 45)
5 -10	76	50	65,6	(54 - 76)
>10	43	39	90,7	(78 - 97)

Table 5. Required F_IO_2 relative to mortality

F_IO_2	n	died	%	(confidence limits) %
0,5	206	84	40,7	(35 - 50)
$\geq$0,5	73	64	87,6	(78 - 94)

Table 6 a. Associated organ dysfunction relative to mortality

patients	n	died	%	(confidence limits) %
with pulmonary disease, only	135	48	35,6	(27 - 44)
with pulmonary disease plus renal dysfunction	93	84	90,3	(82 - 96)
with pulmonary disease plus infectious disease (presumably septicemia)	21	16	76,2	(53 - 92)
with pulmonary disease plus coagulopathy	13	9	69,2	(39 - 91)
with pulmonary disease plus cardio-vascular dysfunction	18	9	50,0	(26 - 74)
with pulmonary disease plus cerebral dysfunction	17	13	76,5	(50 - 93)

Table 6 b. Associated organ dysfunction and the required $F_IO_2 \geq 0,5$ relative to mortality

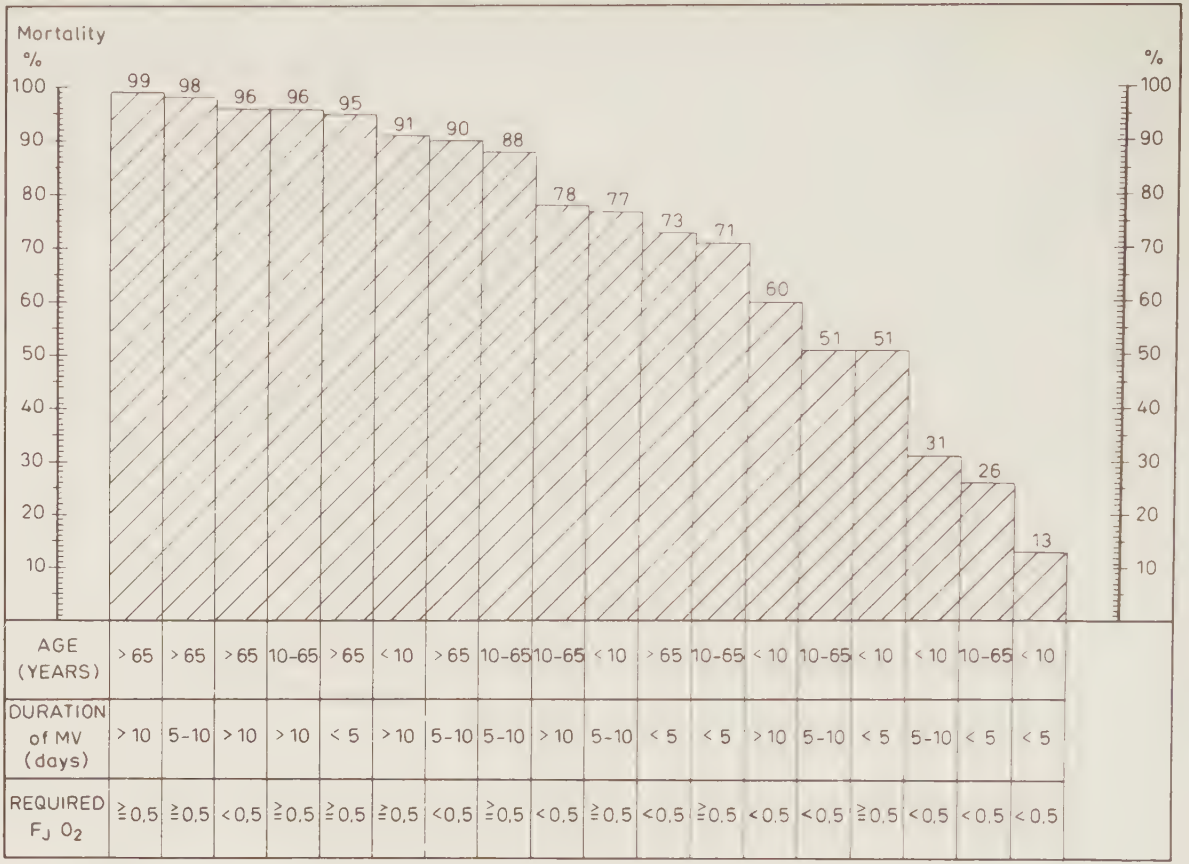
patients	n	died	%	(confidence limits) %
with pulmonary disease, only	50	22	44,0	(30 - 59)
with pulmonary disease plus renal dysfunction	31	30	96,8	(83 - 99)
with pulmonary disease plus infectious disease (presumably septicemia)	6	6	100,0	(54 -100)

Table 7: Distribution of patients and their mortality according to three risk factors: age, duration of MV and required F_IO_2.

age (years)	duration of MV (days)	required F_IO_2	n	died
< 10	< 5	< 0,5	22	1
		≥ 0,5	4	4
	5 - 10	< 0,5	5	1
		≥ 0,5	1	1
	> 10	< 0,5	2	2
		≥ 0,5	1	1
10 - 65	< 5	< 0,5	103	28
		≥ 0,5	16	12
	5 - 10	< 0,5	33	16
		≥ 0,5	27	23
	> 10	< 0,5	19	16
		≥ 0,5	14	13
> 65	< 5	< 0,5	13	12
		≥ 0,5	2	2
	5 - 10	< 0,5	6	6
		≥ 0,5	3	3
	> 10	< 0,5	2	2
		≥ 0,5	5	5
	Total		279	148

Fig. 1:

Estimated mortality rates based on a log linear model relative to the combination of risk factors: Age, duration of mechanical ventilation (MV) and required fraction of inspired oxygen ($F_J O_2$).



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Lebenslauf

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